Remarks

Amendments

Amendments to the specification and claims have been made pursuant to recommendations by the Examiner in the Office action of September 28, 2000, or to obviate objections or provide clarification based on comments contained in the Office action. Claims 3, 4, 6 and 9 have been canceled without prejudice. New claims 12-14 find support, *inter alia*, at pages 7-9 of the specification. No new matter has been added.

Rejection under 35 U.S.C. Sec. 112, Par. 1

Applicants have made the important discovery that use of the alpha subunit of the epithelial sodium channel gene to produce transgenic mammals containing such constructs leads to significantly enhanced production of stretch-activated cation channel, a protein implicated in new bone growth. Applicants have provided key details of the creation of the transgene (see application, e.g., pp. 6-9) and, as they are encouraged to do, have provided additional details regarding matters which are routine to those skilled in the art by incorporating by reference texts and articles where such manipulations are fully set out. See for example, Ausubel et al., "Short Protocols in Molecular Biology," at p.6 and references cited at p.7.

Applicants respectfully traverse the rejection of claims 2-7 and 9 under 35 U.S.C. 112, first paragraph under the written description requirement. Applicants urge that as amended those skilled in the art would appreciate that applicants had possession of the invention as claimed. Claims 2 and 7 have been amended to clarify that such transgenic mammals of these claims are murines. Hence this objection is moot. Claims 3 and 4 have been cancelled also rendering moot the written description rejection of these claims contained at pp. 3-5 of the subject Office action. Accordingly, applicants urge that the rejection be withdrawn.

Applicants also respectfully traverse the rejection of claims 1-11 under 35 U.S.C., first paragraph, for asserted lack of enablement. The pending claims are directed to transgenic non-human mammals capable of enhanced expression of stretch-activated cation channel in osteoblasts (claims 1, 5 and 12), transgenic murines capable of such enhanced expression (claims 2, 7, 13 and 14) and to methods of producing such mammals (claims 8, 10 and 11).

In support of the enablement rejection, the Office asserts that (1) not enough information is provided to enable practicing the invention as to various transgene

constructs for murines, and (2) that for other non-human animals, the art at the time of the invention was too unpredictable to create the claimed transgenic animals without undue experimentation.

It should be beyond dispute that creation of transgenic murines is now routine, and that applicants have provided the necessary information to incorporate nucleotide constructs capable of enhanced expression of the stretch-activated cation channel in murines given the high level of knowledge in this art. Hence, claims 2, 7, 13 and 14 as to murines should be allowed over this rejection. A variety of promoters and vector backbones may be used in such a construct, and the selection of these features and there appropriate manipulation are well within the skill of the art. The fact that skilled artisans could select constructs that would not work, as detailed by the Office, does not provide a basis for rejection. "It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination." *Ex parte Cole*, 223 USPQ 94, 95-96 (BPAI 1983). Moreover, a specific phenotype demonstrating enhanced stretch-activated cation channel activity (minimum increase, 31%) as well as a method of detecting same is disclosed in the specification. See p.9.

Applicants' application should not be viewed in a vacuum. A patent application is entitled to rely on the knowledge of the skilled artisan and need not disclose what is already know in the art. *See In re Wands,* 8 USPQ2d 1400 (Fed.Cir. 1988); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81 (Fed.Cir. 1986). A patent need not teach and preferably omits, what is well know in the art. *In re Buchner*, 18 USPQ 2d 1331, 1332 (Fed.Cir. 1991).

Applicants also traverse the suggestion that the art as to non-murine, non-human transgenic mammals was so unpredictable as to render non-enabled applicants' broader claims. Applicants disclose that the osteoblast cell activity and structure are very similar among mammals, making the disclosed transformation procedures amenable to use with other non-human mammals. See application, p.7, l.5 et seq. Applicants respectfully urge that the Office action confuses undue experimentation with the amount of experimentation in making the enablement rejection. The Office cites various references which show that transgene integration in species other than murines is inefficient, and that, on a percentage basis, successful incorporation is low. That does not equate with unpredictability or undue experimentation. To the contrary, is is recognized that "transgenic sheep, goats, pigs and cattle are now routinely made . . ." Murray, et al.,"Genetic engineering and cloning may improve milk, livestock production," *California Agriculture,* 57-65 (July-August 2000) at p. 57. Similarly, *see Cameron,*

"Recent Advances in Transgenic Technology," *Molecular Biotechnology*, at pp. 253-254 (1997), cited in the Office action. That efficiency is low and cost high does not make such procedures non-routine. The test for "undue" experimentation "is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine . . ." *In re Wands*, 858 F.2d 731, 737 (Fed.Cir. 1988).

For the reasons discussed above, applicants respectfully urge that the enablement rejection for all pending claims be withdrawn.

Rejection under 35 U.S.C. Sec. 112, Par. 2

Applicants respectfully traverse the rejection of claims 1-11 under 35 U.S.C. Sec. 112, par.2 as being indefinite. Claims 3, 4, 6 and 9 have been cancelled without prejudice rendering the rejection as to such claims moot. As to each other claim, applicants have incorporated amendments addressing the specific recommendations of the Examiner, thereby obviating the basis for such rejections under Sec. 112, par. 2. Accordingly, applicants urge that the rejection under Sec. 112, par. 2 be withdrawn.

Rejection under 35 U.S.C. Sec. 102

Applicants respectfully traverse the rejection of claims 1, 2 and 5-7 under 35 U.S.C. 102(b) as being anticipated by Hummler et al. (*Experientia*, 50:A40, Abstract #S12-13, 1994) or alternatively, over Hummler et al. (*Experientia*, 51:A7, Abstract #S03-15, 1995). Similarly, applicants respectfully traverse the rejection of claims 1, 2, 5-7 under Sec. 102(b) as being anticipated by Hummler et al. (*Proc. Natl. Sci. USA,* 94:11710-11715, October, 1997), and traverse the rejection of claims 1, 2, 5, 7 and 11 under Sec. 102(b) as being anticipated by Hummler et al. (*Nature Genetics*, 12:325-328, 1996). Claim 6 has been canceled, so the rejection is moot. Applicants urge that the remaining claims, as amended, clearly distinguish over the cited references. None of the cited Hummler references disclose transgenic non-human mammals, murines or methods of making same wherein the animals have the capability for enhanced expression of stretch-activated cation channels in osteoblasts. Accordingly, these rejections should be withdrawn.

Since claims 3 and 4 have been canceled, the various rejections recited in the Office action of these claims are rendered moot.

Rejection under 35 U.S.C. Sec. 103(a)

Applicants respectfully traverse the rejection of claims 8 and 10 under 35 U.S.C. 103(a) as being unpatentable over Hummler et al. (*Proc. Natl. Acad. Sci. USA*, 94:11710-11715, October, 1997) together with Kizer et al. (*Proc. Natl. Acad. Sci. USA,* 94:1013-1018, February, 1997). As amended, the claims clearly are not suggested by any combination of the references. Hummler et al. sought to create a mouse model for the renal salt-wasting syndrome pseudohypoaldosteronism, type 1 (PHA-1), and in connection therewith, developed a mouse with a markedly reduced expression of α-rENaC. Hummler et al. were engaged in renal studies, were focused on the role of alpha-rENaC in sodium reabsorption, and provide no disclosure whatsoever as to osteoblasts. Hence, Hummler et al. provide no teaching or motivation regarding transgenic mammals with enhanced expression of stretch-activated cation channel, particularly in osteoblasts, as disclosed and claimed by applicants. Accordingly, Hummler fails as a primary reference. Moreover, there is a complete lack of motivation, other than hindsight, to combine Kizer et al. with Hummler et al., given there highly disparate focus. Accordingly, Kizer et al. clearly fails to make up for the deficiencies of Hummler et al. Hence, applicants respectfully urge that this rejection be withdrawn.

Favorable reconsideration of this application, as amended, is respectfully requested. A check for $445.00 for a three month extension of time is enclosed. The Commission is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,

G. Harley Blosser, Reg. No. 33,650
SENNIGER, POWERS, LEAVITT & ROEDEL
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

Express Mail No. EL 732089842 US

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Please delete the sentence at lines 6-7 of page 1 beginning:

"The contents of Applicant's provisional applications 60/110,932 and 60/111,676 are herein incorporated by reference."

In the Claims:

1. (amended) A transgenic non-human [animal] mammal comprising a nucleotide construct capable of [altered] enhanced expression of [α-RENAC] stretch-activated cation channel in osteoblasts relative to a wild-type littermate.

2. (amended) The [animal] mammal of claim 1 wherein the [animal] mammal [further comprises] is a murine.

5. (amended) A transgenic non-human [animal] mammal which has at least one osteoblast cell which contains a recombinant DNA sequence which includes one of the following nucleotide sequences:

a) the nucleotide sequence of SEQ ID NO: 1, or its complement, or any contiguous portion of the nucleotide sequence or complement which is at least 36 nucleotide residues in length;

b) a nucleotide sequence which has at least 80% homology with SEQ ID NO: 1; and

c) any contiguous portion of the nucleotide sequence of (b) which is at least 36 nucleotide residues in length,

and which at least one osteoblast cell is capable of enhanced expression of stretch-activated cation channel relative to such cell without the recombinant DNA sequence.

7. (amended) The [animal] mammal of claim 5 wherein the [animal] mammal [further comprises] is a murine.

8. (amended) A method of producing a non-human mammal with [altered] enhanced expression of [α-rENaC] stretch-activated cation channel in osteoblasts relative to a wild-type littermate comprising:

a) providing a vector construct containing a [transgenic] transgene encoding a protein having [α-rENaC] stretch-activated cation channel activity; and

b) incorporating the vector construct into the genome of the non-human mammal such that the non-human mammal has [altered] enhanced expression of [α-rENaC] stretch-activated cation channel in osteoblasts.

10. (amended) A method of producing [a] progeny of a non-human mammal heterozygous for [an α-rENaC] a stretch-activated cation channel transgene comprising:

a) mating a first non-human mammal with a second non-human mammal, wherein the first non-human mammal expresses [altered] enhanced levels of stretch-activated cation channel in osteoblasts relative to a wild-type litter mate, and wherein the second non-human mammal expresses normal levels of stretch-activated cation channel in osteoblasts; and

b) selecting progeny [derived] obtained from said mating of step a) which are heterozygous for the transgene.

11. (amended) A method of producing [a] progeny of a non-human mammal homozygous for [the α-rENaC] a stretch-activated cation channel transgene comprising:

a) mating a first non-human mammal with a second non-human mammal, wherein the first non-human mammal and the second non-human mammal express [altered] enhanced levels of stretch-activated cation channel in osteoblasts relative to a wild-type litter mate; and

b) selecting progeny [derived] obtained from said mating of step a) which are homozygous for the transgene.